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*Published in:*  
British Journal of Clinical Pharmacology

*DOI:*  
[10.1111/bcp.13205](https://doi.org/10.1111/bcp.13205)

*Publication date:*  
2017

*Licence:*  
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*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

*Citation for published version (APA):*  
Wei, L., Ratnayake, L., Phillips, G., McGuigan, C. C., Morant, S. V., Flynn, R. W., Mackenzie, I. S., & MacDonald, T. M. (2017). Acid-suppression medications and bacterial gastroenteritis: a population-based cohort study. *British Journal of Clinical Pharmacology*, 83(6), 1298-1308. <https://doi.org/10.1111/bcp.13205>

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# DRUG SAFETY

## Acid-suppression medications and bacterial gastroenteritis: a population-based cohort study

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**Received** 1 June 2016; **Revised** 25 October 2016; **Accepted** 21 November 2016

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**Keywords** acid-suppression medications, bacterial gastroenteritis, cohort study

### AIMS

To investigate whether acid-suppression medicines (ASMs) increase the risk of bacterial gastroenteritis.

### METHODS

A population-based, propensity-score matched cohort study using a record-linkage database in Tayside, UK. The study consisted of 188 323 exposed to ASMs (proton-pump inhibitors and histamine-2 receptor antagonists) and 376 646 controls (a propensity-score matched cohort from the rest of population who were not exposed to ASMs) between 1999 and 2013. The main outcome measure was a positive stool test for *Clostridium difficile*, *Campylobacter*, *Salmonella*, *Shigella* or *Escherichia coli* O157. The association between ASMs and risk of bacterial gastroenteritis was assessed by a Cox regression model.

### RESULTS

There were 22 705 positive test results (15 273 *C. difficile* [toxin positive], 6590 *Campylobacter*, 852 *Salmonella*, 129 *Shigella* and 193 *E. coli* O157, not mutually exclusive) with a total of 5 729 743 person-years follow up time in Tayside, 1999–2013. The adjusted hazard ratios for culture positive diarrhoea for the proton-pump inhibitors and histamine-2 receptor antagonists exposed vs. unexposed cohort were 2.72 (95% confidence interval [CI] 2.33, 3.17) during follow-up time for samples submitted from the community and 1.28 (95% CI 1.08, 1.52) for samples submitted from hospitals. Compared with the unexposed cohort, patients in the exposed group had increased risks of *C. difficile* and *Campylobacter* [adjusted hazard ratios of 1.70 (95% CI 1.28, 2.25), 3.71 (95% CI 3.04, 4.53) for community samples, and 1.42 (95% CI 1.17, 1.71), 4.53 (95% CI 1.75, 11.8) for hospital samples, respectively].

### CONCLUSIONS

The results suggest that community prescribed ASMs were associated with increased rates of *C. difficile* and *Campylobacter* positive gastroenteritis in both the community and hospital settings.

## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Acid-suppression medications are increasingly being prescribed in both the community and hospital settings in the UK.
- Omeprazole was the most commonly prescribed acid-suppression medication by volume in Scotland in the past 2 years.
- Acid-suppressing drugs have been implicated as a risk factor for bacterial gastroenteritis but meta-analyses have provided inconsistent findings.

## WHAT THIS STUDY ADDS

- In a population-based study with good ascertainment of exposure and outcome, acid-suppression medications were associated with increased rates of culture-positive stool tests for presumed diarrhoea submitted from both the community and hospitals.
- The risk of positively testing stool samples for *C. difficile* and *Campylobacter* was increased with exposure to acid-suppressing medications.
- Whilst acid-suppression therapy is often considered relatively free from adverse effects, patients who are taking acid-suppression medications need to be aware of the increased risks of bacterial gastroenteritis.

## Introduction

Bacterial gastroenteritis continues to be a major global challenge with increased morbidity, mortality, and significant public health and social implications. *Clostridium difficile* is more common in the hospital setting than in the community [1] although community-acquired *C. difficile* infection is increasing [2]. *C. difficile* is one of the most prevalent organisms causing healthcare associated infections in Scotland, with 3634 cases in patients aged 65 years and over in 2009 with an annual overall rate for 2009 of 0.71 per 1000 total occupied bed days [3]. *Campylobacter*, *Salmonella*, *Shigella* and *Escherichia coli* O157 account for the majority of cases of bacterial pathogens identified in the community setting in Scotland, with more than 7500 reports in 2009 and the overall rate of reported *Campylobacter* infection in 2009 was 123.4 per 100 000 [4]. Widely documented risk factors for *Campylobacter*, *Salmonella*, *Shigella* and *E. coli* O157 include consumption of undercooked meat, contact with animals and foreign travel. For *C. difficile*, common predisposing factors include old age, antibiotic use, hospitalization, underlying comorbid illnesses and gastrointestinal procedures. There are two classes of acid-suppression medication: proton-pump inhibitors (PPIs), which stop acid secretion by inhibiting proton pumps located in the canalicular membrane of the parietal cell; and histamine-2 receptor antagonists (H2RAs), which target histamine, one of the primary regulators of acid secretion. More recently, acid-suppression medications have been implicated as a risk factor for bacterial gastroenteritis [5–18]. However, other studies have found no association between these bacterial infections and use of PPIs [19–23]. Acid suppression medications, such as PPIs, are increasingly being prescribed in both the community and hospital settings. The aim of this study was to investigate whether acid-suppression medicines increase the risk of bacterial gastroenteritis.

## Methods

### Study design

This was a cohort study in which patients exposed to acid-suppression drugs were compared to a matched cohort of

patients not exposed to these drugs during the study period of January 1999 to February 2013. The cohorts were drawn from the Tayside Medicines Monitoring Unit (MEMO) database, which covers a geographically compact population and serves about 400 000 patients, mixed urban and rural, in the National Health Service in Scotland, 97% of whom are Caucasian [24]. The National Health Service is tax-funded, free at the point of consumption, and covers the entire population. In Tayside, there is almost no health care delivered without the National Health Service and there is a low rate of patient migration (<3% of patients aged ≥60 years left the Tayside region over a 5-year period from 2004 to 2008). This population-based, record-linkage database contains several datasets including all dispensed community prescriptions, hospital discharge data, demographic data, laboratory results including blood, urine and stool tests, and other data, all of which are linked by a community health index number that is unique to each patient.

### Study population

The study population consisted of residents of Tayside registered with a general practitioner (GP) between January 1999 and February 2013. It was a dynamic population that included people who registered with a GP, died or left Tayside during the study period. Patients with inflammatory bowel disease (IBD), defined as those hospitalized for or on medication for IBD, bowel cancer or gastrointestinal surgery, were excluded. Patients with <30 days' follow-up were also excluded from the study.

### Exposed cohort

The exposed cohort consisted of patients who received at least one dispensed prescription of acid-suppression drugs, either PPIs or H2RAs, during the study period. An index date was defined for each patient as the date of first exposure, or 1<sup>st</sup> January 1999 if the exposure period spanned this date.

### Control cohort

A pool of potential control patients was created by assigning index dates at random to unexposed patients by incidence density sampling from the distribution of index dates in the exposed cohort. Exposed patients could also be included as potential controls, with their follow-up time censored at the

first prescription for an acid-suppressing drug. A control cohort was created by matching unexposed patients to each exposed patient within deciles of a propensity score distribution, and selecting two patients randomly. The propensity scores were the probabilities of exposure to acid-suppressing drugs estimated from a logistic regression model with the covariates evaluated on each patient's index date. The details of covariates are listed in the next section.

### Outcomes and covariates

The primary outcome was bacterial gastroenteritis defined as the composite of a stool test that was positive for *C. difficile*, *Campylobacter*, *Salmonella*, *Shigella* or *E. coli* O157 (culture-positive tests). The secondary outcomes were individual components of the composite of the primary outcome, culture negative tests, and any completed stool test (a surrogate for symptoms of diarrhoea). A stool sample originating from primary care was classified as a community sample and one originating from a hospital in-patient source was classified as a hospital sample.

Covariates included sex and the following, evaluated on each patient's index date: socioeconomic status measured by the Scottish Index of Multiple Deprivation [25], history of cardiovascular disease, diabetes mellitus, pulmonary disease, renal disease, liver disease, cancer (excluding bowel cancer) and human immunodeficiency virus/acquired immune deficiency syndrome. Time dependant covariates were: age, calendar year, season (quarters), hospitalization for any reason, hospitalization with peptic ulcer, hospitalization with another infection, recent discharge (in the last 28 days) and community antibiotic use.

### Definition of acid-suppression therapy exposure

Exposure periods for PPIs and H2RAs were calculated separately. The proportions of acid-suppression exposure were 59% for PPI and 41% for H2RAs. The quantity of drug supplied and the dosing instructions were used to estimate the length

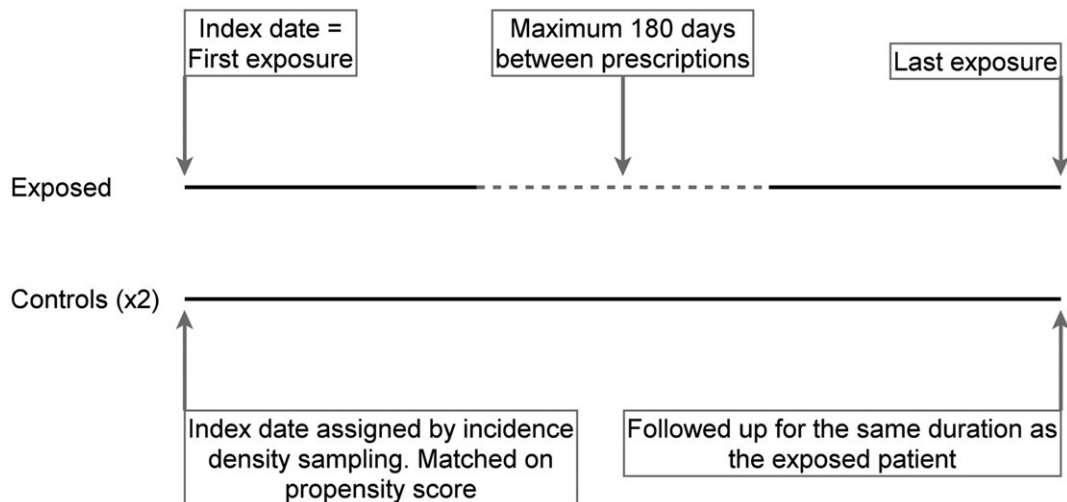
of exposure provided by each prescription. If an exposure period was followed by another prescription within 180 days it was treated as an unbroken period of exposure (a conventional and commonly used cut-off point in drug safety research), otherwise treatment was deemed to have discontinued (Figure 1). A mean daily dose was calculated over each exposure period (the sum of the daily doses on each prescribed day divided by the total length of the exposure period). PPI doses were normalized to esomeprazole by multiplying by: 1 for pantoprazole and omeprazole; 4/3 for lansoprazole, and 2 for rabeprazole. H2RA doses were standardized to cimetidine by multiplying by 8/3 for nizatidine and ranitidine and by 20 for famotidine [26, 27]. Tertiles of each normalized dose distribution (18 and 25 mg day<sup>-1</sup> for PPI, 747 and 1190 mg day<sup>-1</sup> for H2RA) were used to define categorical low, medium and high dose variables for each drug class.

### Statistical analysis

Proportional hazard models, stratified by GP practice, were fitted to the time from each patient's index date to an outcome. The proportional hazard model assumption was checked before the analysis. Time-dependent variables listed in the covariates section were built into the models. The primary analysis compared the exposed subjects while they continued acid-suppression therapy with their unexposed controls over the same length of time from their respective index dates. A further set of analyses included the exposed patients only, and were designed to assess dose responses. Population attributable risks were calculated by study year for hospital and community settings. All analyses were carried out using SAS version 9.3.

### Sensitivity analyses

Losec, a registered trademark name of omeprazole was made available over-the-counter (OTC) in low dose for limited duration in 2004 and H2 antagonists were also made available OTC in low dose for limited duration in 1994. We had no



**Figure 1**

Illustration of the exposure time

record of such use. However, patients aged 60 years or older were not charged for prescribed drugs and were unlikely to purchase them OTC. To minimize any bias due to unrecorded exposure to omeprazole we did two sensitivity analyses, one with follow-up time censored at the beginning of 2004, and another restricted to patients aged 60 years or more.

The primary analysis revealed a very large excess risk associated with hospitalization, which may have masked other effects. Therefore, in unplanned sensitivity analyses we censored each patient at their first admission to hospital following their index date. Further sensitivity analyses excluded: (i) prevalent users; (ii) patients with only one prescription of acid-suppression drugs; and (iii) the first 15 or 30 days after index date.

We also examined heterogeneity in the effects of drug exposure between practices, and conducted a meta-analysis to obtain a pooled estimate allowing for between-practice variations.

### Ethical approval

Ethical committee approval was obtained from the Tayside Committee on Medical Research Ethics. MEMO is part of Farr Institute @ Scotland.

## Results

### Study population

We found 571 239 distinct patients registered with Tayside practices between 1999 and 2013. We excluded 2280 patients with <30 days follow-up in the study period, and 16 806 patients with IBD or bowel cancer. Among the remaining 552 153 eligible patients 149 636 stool tests were conducted in a total of 5.7 million patient years follow up. There were 22 705 positive test results (15 273 *C. difficile* [toxin positive], 6590 *Campylobacter*, 852 *Salmonella*, 129 *Shigella* and 193 *E. coli* O157, not mutually exclusive).

The exposed cohort consisted of 188 323 patients exposed to acid-suppression drugs during the study period. We identified 376 646 control patients, two for each exposed patient selected randomly from unexposed patients in the same practice and the same decile of the propensity score distribution. The baseline covariates for each cohort are summarized in Table 1.

### Primary analysis

The hazard ratios (HRs) obtained from the primary analysis (i.e. for culture-positive diarrhoea in patients exposed to acid-suppressing drugs vs. an unexposed cohort) are shown in Figure 2. The HR for the exposed vs. unexposed cohort was 2.72 (95% confidence interval [CI] 2.33, 3.17) for samples submitted from the community. However, there was a smaller risk associated with exposure to community prescribed acid-suppressing drugs for samples originating in hospitals (HR = 1.28 [95% CI 1.08, 1.52]). Hospital in-patients had a very high risk of culture-positive diarrhoea when compared to out-patients (HR = 89.7 [95% CI 72.3, 111.2]). If the reason for hospitalization was associated with infection the risks

were even greater (HR = 11.6 [95% CI 9.91, 13.4]) relative to hospitalization for other reasons.

The risk was also elevated in patients with human immunodeficiency virus/acquired immune deficiency syndrome or pulmonary or renal disease at baseline. There was no clear evidence of a trend with socioeconomic status. There was an increase in the rate of detection of culture-positive diarrhoea between 1999 and 2006, and some evidence of a small decline since 2009. Risk was higher in the summer months (April to September) than in the first quarter of the year. There was little evidence of a trend with age, although patients aged 20–29 years had higher rates than other age groups.

### Secondary and sensitivity analyses

Estimates of the HR for exposed vs. unexposed patients in subgroup and sensitivity analyses are summarized in Table 2. The HR for samples from the community was slightly lower in older patients, as would be expected if exposure to OTC omeprazole had diluted the apparent effect of acid-suppression therapy. However, it was also lower before OTC omeprazole became available in 2004. The lowest HR was 1.29 (95% CI 1.06, 1.57) for culture-positive samples from hospitals for patients aged over 60 years old. The exclusion of prevalent users, the first 15 days or 30 days after the index date and patients with only one prescription had little effect on the HRs for culture-positive samples (Table 2). The highest HR was 4.53 (95% CI 1.75, 11.8) for samples from hospital for *Campylobacter*.

The HRs associated with acid-suppression with *Campylobacter* cases were 3.71 (95% CI 3.04, 4.53) for community samples, where this organism accounted for 63% of tested positive cases, and 4.53 (95% CI 1.75, 11.8) in hospitals, where it accounted for only 6% of tested positive cases. The HRs for *C. difficile* cases were 1.70 (95% CI 1.28, 2.25) from the community and 1.42 (95% CI 1.17, 1.71) from hospital. *C. difficile* accounted for 92% of positive stool cases in hospitals and 27% of tested positive cases in the community. There were too few cases of *Salmonella*, *Shigella* and *E. coli* O157 to allow analyses of these organisms individually. The HR for tested negative cases was 3.30 (95% CI 3.10, 3.52) in the community and 1.33 (95% CI 1.25, 1.42) in hospital.

Censoring follow-up time at first hospitalization generally yielded HRs similar to or slightly higher than those obtained in the community without censoring.

### Dose response relationship

Figure 3 shows the association between dose and primary and secondary outcomes. There was a clear dose response relationship between acid-suppression medication and culture negative outcomes. Compared with medium dose, the HRs for low dose and high dose were 0.90 (95% CI 0.86, 0.95) and 1.06 (95% CI 1.02, 1.11) for PPIs; and 0.95 (95% CI 0.84, 1.06) and 1.16 (95% CI 1.07, 1.27) for H2RA, respectively. These findings may support a causal relationship between acid-suppressing medications and symptoms that lead to stool culture. However, we did not observe a dose-response relationship for stool tested positive diarrhoea due to *C. difficile* and *Campylobacter*.

**Table 1**

Distribution of baseline covariates in the exposed cohort and a control cohort matched on a propensity score for exposure

		Exposed cohort		Control cohort	
		<i>n</i>	%	<i>n</i>	%
<b>Total patients</b>		188 323	100.0	376 646	100.0
<b>Sex</b>	Female	103 468	54.9	207 520	55.1
	Male	84 855	45.1	169 126	44.9
<b>Age, years</b>	<10	1707	0.9	15 884	4.2
	10–19	8787	4.7	18 705	5.0
	20–29	18 824	10.0	30 667	8.1
	30–39	23 849	12.7	43 905	11.7
	40–49	29 431	15.6	57 551	15.3
	50–59	31 377	16.7	62 314	16.5
	60–69	32 683	17.4	64 970	17.2
	70–79	26 490	14.1	52 514	13.9
	80–89	12 800	6.8	25 926	6.9
	≥90	2375	1.3	4210	1.1
<b>Socioeconomic status</b>	Unknown	916	0.5	2591	0.7
	1 (most deprived)	57 231	30.4	115 362	30.6
	2	36 554	19.4	72 602	19.3
	3	32 538	17.3	64 737	17.2
	4	41 936	22.3	83 610	22.2
	5 (most affluent)	19 148	10.2	37 744	10.0
<b>Year of index date</b>	1999	39 611	21.0	93 733	24.9
	2000	13 970	7.4	28 302	7.5
	2001	12 496	6.6	24 925	6.6
	2002	10 285	5.5	20 247	5.4
	2003	10 522	5.6	20 192	5.4
	2004	10 918	5.8	20 024	5.3
	2005	11 150	5.9	20 673	5.5
	2006	11 465	6.1	20 993	5.6
	2007	10 365	5.5	19 440	5.2
	2008	10 494	5.6	19 507	5.2
	2009	10 318	5.5	19 192	5.1
	2010	10 576	5.6	20 020	5.3
	2011	11 557	6.1	21 785	5.8
	2012	12 598	6.7	23 947	6.4
	2013	1998	1.1	3666	1.0
<b>Disease history on index date</b>	Cardiovascular disease	110 101	58.5	222 892	59.2
	Diabetes mellitus	10 165	5.4	19 075	5.1
	Pulmonary disease	4316	2.3	8019	2.1
	Renal disease	1606	0.9	2610	0.7
	Liver disease	927	0.5	1447	0.4
	Cancer	6773	3.6	12 429	3.3
	HIV/AIDS	76	0.0	119	0.0

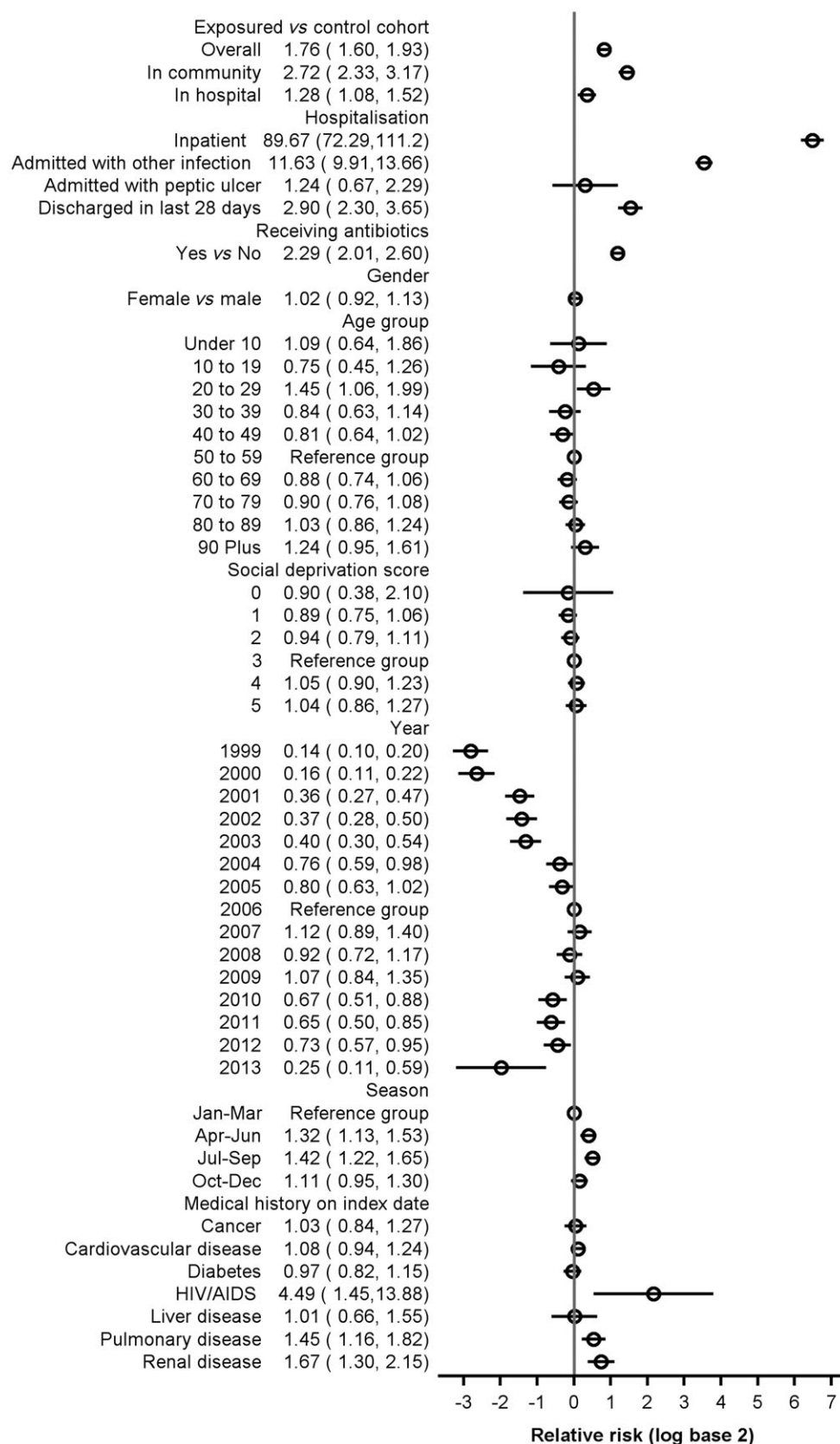
HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome

### Practice heterogeneity

The hazard ratios for the effect of acid-suppression on stool test-positive diarrhoea rates in the community estimated for each practice separately. Time-to-event analyses with time dependent covariates in very large datasets are not always feasible because of the computing resources required. Although we were able to conduct overall analyses

in this study, we also used the methodology of meta-analyses to pool the HRs from individual practices for comparison. The test for heterogeneity was statistically significant ( $P = 0.004$ ), but there were no extreme outliers and the scale of the over-dispersion was not large. The pooled HR was 2.85 (95% CI 2.39, 3.40), assuming a random effects model. This is close to the value obtained



**Figure 2**

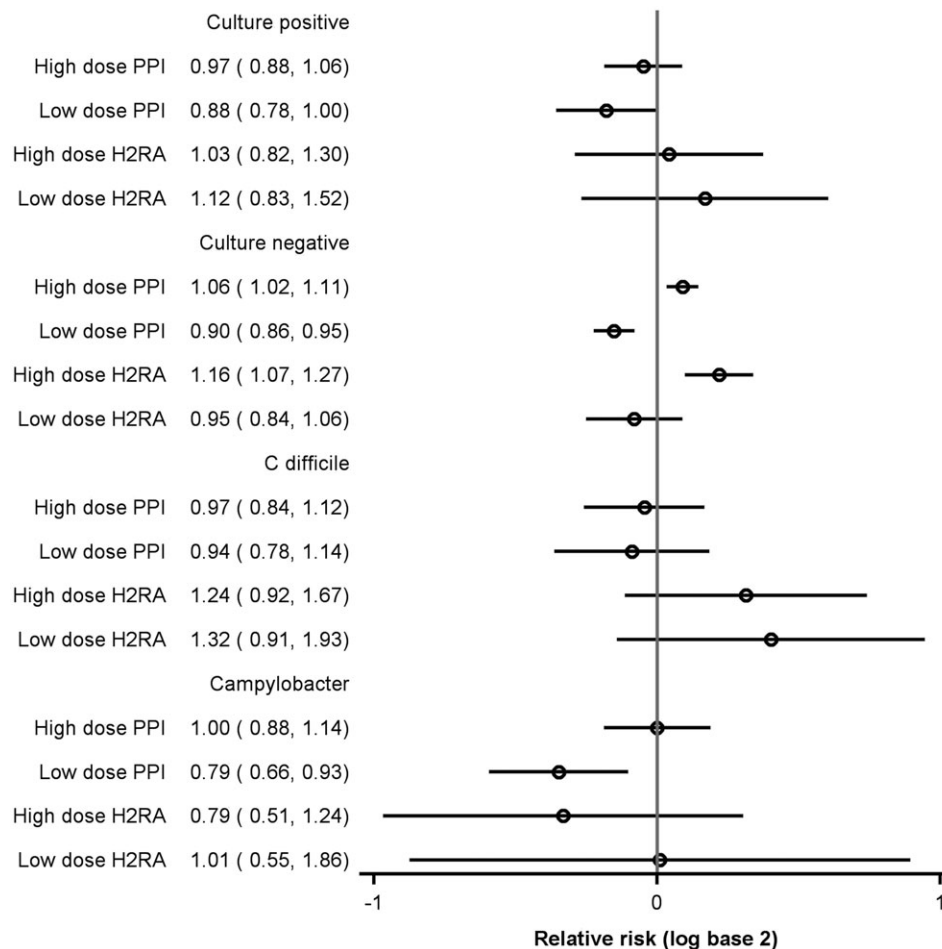
Adjusted hazard ratios for culture-positive stool tests in patients registered with Tayside practices, 1999 to 2013

**Table 2**

Hazard ratios for the secondary outcomes in patients exposed to acid-suppressing drugs vs unexposed matched controls

	Follow-up including hospital stays		Censored at first admission
	Community samples	Hospital samples	
<b>Culture positive diarrhoea</b>	2.72 (2.33, 3.17)	1.28 (1.08, 1.52)	3.23 (2.71, 3.86)
<b>Before 2004</b>	1.73 (1.07, 2.79)	1.54 (1.16, 2.05)	1.77 (1.01, 3.10)
<b>Patients aged ≥60 years</b>	2.00 (1.63, 2.47)	1.29 (1.06, 1.57)	2.42 (1.83, 3.22)
<b>Incident ASM users only</b>	2.97 (2.53, 3.50)	1.34 (1.10, 1.63)	3.44 (2.82, 4.16)
<b>Patients with &gt;1 ASM prescription</b>	3.26 (2.35, 4.46)	1.20 (0.87, 1.67)	2.89 (2.17, 3.84)
<b>Events &gt;15 days after index date</b>	2.52 (2.14, 2.96)	1.18 (0.99, 1.40)	3.17 (2.64, 3.80)
<b>Events &gt;30 days after index date</b>	2.77 (2.33, 3.30)	1.24 (1.03, 1.49)	3.34 (2.77, 4.03)
<b><i>Clostridium difficile</i></b>	1.70 (1.28, 2.25)	1.42 (1.17, 1.71)	2.00 (1.25, 3.19)
<b><i>Campylobacter</i></b>	3.71 (3.04, 4.53)	4.53 (1.75, 11.8)	3.76 (3.05, 4.64)
<b>Culture negative diarrhoea</b>	3.30 (3.10, 3.52)	1.33 (1.25, 1.42)	3.38 (3.15, 3.63)
<b>Diarrhoea (any stool sample)</b>	3.26 (3.07, 3.46)	1.32 (1.24, 1.40)	3.36 (3.14, 3.59)

Adjusted for all covariates listed in the Methods section

**Figure 3**

Adjusted hazard ratios for high and low vs. medium doses of acid-suppressing drugs



from the primary analysis and with a similar confidence interval [2.72 (95% CI 2.33, 3.17)].

### Attributable risk

The use of acid-suppressing drugs approximately doubled over the study period (Table 3). In 1999, 5.3% of patient follow-up time in the community and 18.6% of follow-up time for hospitalized patients were in the exposed cohort. In 2012, the exposure rates were 11.6% in the community and 35.5% in hospitals. Our estimates of exposure rates in hospital were based on the assumption that patients continued exposure to community prescribed drugs in hospital and do not include prescriptions issued in hospital.

We have estimated attributable events in the community and in hospitals in each year of the study. In 2012, for example, 578 events occurred during exposure in the community and we estimate that  $578 \times (2.72-1)/2.72 = 366$  of these (27.1% of all cases in that year) were attributable to exposure. Had there been no exposure to acid-suppressing drugs the expected event rate would have been 2.46 per 1000 patient years (ptpy) instead of 3.38 ptpy. The contribution of exposure to the observed population event rate was therefore 0.92 ptpy.

## Discussion

We have found that acid-suppression medicines were associated with increased risks of bacterial gastroenteritis. Patients in the community had higher risk of diarrhoea associated with acid-suppression medicines use than patients in hospitals. The sensitivity analysis showed that the results were unlikely to be confounded by other factors.

The supposed higher risk of *C. difficile* infection in PPI users is based on the increased ability of the acid-resistant spore to convert to the vegetative form and survive in a hypo-acid environment [28]. Gastric acid may not effectively kill *C. difficile* but could alter the growth of other commensal bowel flora. Increasing acid-suppression has previously been associated with increased risk of *C. difficile* infections with PPI exposure [17, 29] but a meta-analysis found that the quality of evidence was poor. In a separate meta-analysis, the same authors found that H2RA exposure was associated with *C. difficile* infection (pooled effect estimate: 1.44, 95% CI [1.22–1.70]), this effect being strongest in hospitalized patients [30]. This is supported by our data and other meta-analyses [16]. Other authors have concluded that PPI exposure is associated with a higher risk of *C. difficile* than H2 antagonist exposure.

Bavishi and Dupont [31] reviewed the evidence for the association between PPIs and bacterial gastrointestinal infection and concluded that there was evidence to support the association. However, in general, previous studies lacked access to all laboratory tests on a population basis. It was also suggested that the role of the gut microbiome in arresting pathogen colonization and growth is important for protection against *C. difficile* infection [32, 33]. Seto and colleagues [33] hypothesized that PPI use affected the distal gut microbiome over time and they did a study in nine healthy human subjects and five treatment-naïve subjects with *C. difficile*

infection. They found that PPIs resulted in decreases in observed operational taxonomic unit counts, and decreases in observed species counts which were reversible after cessation of PPI usage within 1 month. This finding may be a potential explanation for the association between prolonged PPI usage and *C. difficile* infection incidence [33]. PPI use was also linked with an increased risk of serious infections including gastroenteritis in veterans with decompensated cirrhosis [34]. However, among hospitalized adults with *C. difficile*, receipt of PPIs concurrent with *C. difficile* treatment was not associated with *C. difficile* infection recurrence [35].

A recent study [36] of the association between PPIs and *Campylobacter* and *Salmonella* infections was conducted in the general population of Wales including over one million patients. The study applied a new analysis technique: prior event rate ratio (PERR) adjustment to control both measured and unmeasured confounders (i.e. the unadjusted event rate ratio during the study was adjusted by dividing by the PERR) [37]. They found that the rate of *Campylobacter* and *Salmonella* infections was already at 3.1–6.9 times that of non-PPI patients even before PPI prescription. The adjusted HR was 6.91 (95% CI 5.16, 9.26) for the PPI group when compared with the non-PPI group. However, the ratio of events in the PPI group compared with the non-PPI group using the prior event rate ratio was 1.17 (95% CI 0.74, 1.61) for *Campylobacter* and 1.00 (95% CI 0.5, 1.5) for *Salmonella*. The HRs of *Campylobacter* in our study were 3.71, (95% CI 3.04, 4.53) in the community and 4.53, (95% CI 1.75, 11.8) in hospital and they were significantly higher than the PERR adjusted HR of 1.7. Comparison of our study with the Welsh study should be done with caution as there are several key differences between the studies. Firstly we used a Cox regression model with a time-dependent variable technique to address risk changes including PPI exposure over time. This is an established method in drug safety research. However, the Welsh study applied a relatively new method to get an adjusted HR. Secondly, our study was a propensity matched cohort study with a mean follow-up of 10 years while the Welsh study only used 2 years of data for their cohort study (i.e. the 12-month period before PPI prescription and the 12-month period post-PPI prescription) and the control group was only matched for date with the PPI patients (matched on day, month, year). Thirdly, the Welsh study used prescribed prescriptions for exposure, while our study used dispensed prescriptions which would eliminate primary noncompliance as a previous study showed that some patients do not collect their prescriptions at a pharmacy [38]. The association between *Campylobacter* and PPI use has also been supported by a recent ecological study from The Netherlands and a study from the UK [39, 40]. The high risk for tested negative cases in the community (HR, 3.3) and in hospital (1.33) suggests that acid-suppressing therapy itself may lead to symptoms that result in a stool sample being submitted. In fact, these cases of culture-negative diarrhoea are probably due to an organism that has not been detected, as culture-positive specimens represent only a fraction of infections that actually occur in the community or hospital populations.

Although not the primary reason for carrying out the study, we also found that very high hazards of culture-positive stool samples were associated with recent hospitalization (HR = 89.7 [95% CI 72.3, 111.2]) or hospitalization

Table 3

Population attributable risk of acid-suppression therapy for culture-positive stool tests, 1999 to 2013

	Study population						Periods of exposure						Attributable events							
	Community samples			Hospital samples			Community samples			Hospital samples			Community samples (HR = 2.72)			Hospital samples (HR = 1.28)				
	Patient years	Cases	Rate <sup>a</sup>	Patient years	Cases	Rate <sup>a</sup>	Patient years	%	Cases	Rate <sup>a</sup>	Patient years	%	Cases	Rate <sup>a</sup>	n	% <sup>b</sup>	Δ <sup>c</sup>	n	% <sup>b</sup>	Δ <sup>c</sup>
<b>1999</b>	411 063	169	0.41	1156	111	96.0	21 906	5.3	74	3.38	215	18.6	30	139.5	47	27.7	0.11	7	5.9	5.68
<b>2000</b>	409 187	397	0.97	1127	246	218.3	23 912	5.8	113	4.73	219	19.4	67	305.9	71	18.0	0.17	15	6.0	13.00
<b>2001</b>	405 186	580	1.43	1101	380	345.1	25 870	6.4	268	10.36	220	20.0	136	618.2	169	29.2	0.42	30	7.8	27.02
<b>2002</b>	402 901	605	1.50	1086	466	429.1	24 833	6.2	211	8.50	208	19.2	128	615.4	133	22.1	0.33	28	6.0	25.78
<b>2003</b>	401 435	615	1.53	1063	408	383.8	27 573	6.9	240	8.70	232	21.8	120	517.2	152	24.7	0.38	26	6.4	24.69
<b>2004</b>	402 689	1194	2.97	966	578	598.3	29 574	7.3	465	15.72	234	24.2	188	803.4	294	24.6	0.73	41	7.1	42.57
<b>2005</b>	401 777	1414	3.52	998	587	588.2	32 768	8.2	589	17.97	267	26.8	216	809.0	372	26.3	0.93	47	8.0	47.34
<b>2006</b>	402 192	1633	4.06	1020	704	690.2	34 727	8.6	714	20.56	282	27.6	267	946.8	452	27.6	1.12	58	8.3	57.26
<b>2007</b>	403 100	1949	4.84	1017	926	910.5	36 279	9.0	886	24.42	302	29.7	362	1198.7	560	28.7	1.39	79	8.6	77.86
<b>2008</b>	404 879	1828	4.51	1013	712	702.9	38 183	9.4	715	18.73	310	30.6	275	887.1	452	24.7	1.12	60	8.4	59.38
<b>2009</b>	403 593	1631	4.04	1023	549	536.7	39 768	9.9	705	17.73	323	31.6	191	591.3	446	27.3	1.10	42	7.6	40.84
<b>2010</b>	402 403	1361	3.38	993	314	316.2	41 634	10.4	564	13.54	325	32.7	118	363.1	357	26.2	0.89	26	8.2	25.99
<b>2011</b>	401 127	1304	3.25	954	265	277.8	44 362	11.1	570	12.85	333	34.9	117	351.4	360	27.6	0.90	26	9.7	26.83
<b>2012</b>	399 099	1350	3.38	962	291	302.5	46 101	11.6	578	12.54	351	36.5	118	336.2	366	27.1	0.92	26	8.9	26.83
<b>2013</b>	64 473	116	1.80	160	22	137.5	7586	11.8	38	5.01	57	35.6	8	140.4	24	20.7	0.37	2	8.0	10.94

<sup>a</sup>Cases per 1000 patient years,<sup>b</sup>% of cases,<sup>c</sup>contribution to observed event rate

with an infection (HR = 11.6 [95% CI 9.9, 13.7]) or with community antibiotic use (HR = 2.3 [95% CI 2.0, 2.6]). Thus, the effects of hospitalization and antibiotic use appear to be the dominant associations with culture-positive stool samples. Finally, acid-suppressing therapy showed a dose-dependent association with an increased risk of culture negative sample submission, supporting the hypothesis that these drugs themselves induce diarrhoea that leads to stool sample submission.

Our study has some strengths and limitations. We used a well validated population-based record linkage database with complete ascertainment of all stool samples submitted to the regional laboratory. It was possible to determine the source of the stool samples, whether originating from the community or hospitals. The database contained exposure data on dispensed medications (rather than prescribed medications) thus eliminating misclassification caused by primary non-compliance and we could decode the intended dose and duration of medications. The study population had an excellent roster file that allowed complete ascertainment of subject eligibility over time and record-linkage was deterministic (not probabilistic) resulting in more accurate linkage. We were able to track subjects' membership of individual primary care practices, to measure a social deprivation score and to obtain good data on comorbidities.

A limitation of the MEMO database is that exposure to nonprescription drugs is not recorded, and omeprazole and H2RAs have been available OTC since 2004 albeit in lower doses. There are no culture data for viral causes of diarrhoea, and only a restricted range of bacterial pathogens was investigated in the study. Nonsteroidal anti-inflammatory drug use was not adjusted for in the analysis, but these drugs increase intestinal permeability and may predispose to inflammation or even susceptibility to infection. Parasitic infections were also not included in the study outcome. Also, since MEMO does not have information on disease severity, smoking, body mass index, alcohol and other factors, which might be linked to diarrhoea, we were unable to use them as matching criteria. Although we used a propensity score to build an unexposed cohort using available risk factors, and we adjusted for multiple covariates and carried out sensitivity analyses, we cannot exclude effects due to unrecognized or unrecorded confounding factors. The effect of discontinuing drugs is difficult to assess because the date of discontinuation is estimated from the last known prescription and is subject to error. Short-term effects, in particular, are likely to be underestimated. Our estimates of attributable risk take no account of any effects of discontinuation, and may therefore be underestimates.

In conclusion, acid-suppressing therapy with PPIs or H2RAs increased the risk of both bacterial gastrointestinal infections and culture negative stool samples submitted for presumed diarrhoea. Compared with subjects not taking PPIs or H2RAs, community-prescribed PPIs and H2RAs were associated with increased rates of positive stool samples for *C. difficile* and *Campylobacter* submitted from both the community and hospitals. Whilst acid-suppression therapy is often considered relatively free from adverse effects this present study suggests that there are significant adverse gastrointestinal noninfective and infective consequences of their use.

## Competing Interests

There are no competing interests to declare.

*This study was funded by Chief Scientist Office Scotland (Ref CZG/2/540). The funder had no role in the design, conduct or data interpretation of the study.*

## Contributors

L.W., L.R., G.P., C.C.M. and T.M.M. were involved in conception and design and interpretation of data. L.W. wrote the first draft of the article. S.M. did the statistical analysis. S.M., R.W.F. and I.S.M. were involved in interpretation of data. All authors were responsible for redrafting of the article and approved the final version. L.W. is the guarantor.

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